REMARKS

Reconsideration of the Office Action mailed November 15, 2001, (hereinafter "instant Office Action"), entry of the foregoing amendments and withdrawal of the rejection of claims 18-21 and 23-45, are respectfully requested.

In the instant Office Action, claims 1-45 are listed as pending, claims 1-17 and 22 are listed as being withdrawn from consideration and claims 18-21 and 23-45 are listed as rejected.

Attached hereto as Appendix A is a marked-up version of the changes made to the claims by the current amendments. Appendix A is captioned "**Version with markings to show changes made**". Also attached hereto as Appendix B is a complete set of the claims that will be pending upon entry of the amendments presented herein.

The Examiner has made the restriction requirement final. The claims under prosecution are those of Group VII, claims 18-21 and 23-45, drawn to the compound of claim 18, pharmaceutical composition and method of use, classified in various classes and subclasses depending on the nature of R and R^1.

The Examiner has withdrawn claims 1-17 and 22 as being drawn to a non-elected group. Applicants have cancelled claims 1-17 and 22, without waiver or prejudice to Applicants right to prosecute said claims in a continuation or divisional application.

The Examiner has rejected claims 18-21 and 23-45 under the judicially created doctrine of being drawn to an improper Markush group. The Examiner alleges that:

> [t]he variables R and R^1 are defined in such a way that they keep changing the core of the compound that determines the classification. By changing these values, several patentably distinct and independent compounds are claimed. In order to have unity of invention the compounds must have a "community of chemical or physical characteristics" which justify their inclusion in a common group, and that such inclusion is not repugnant to principles of scientific classification" In re JONES (CCPA) 74 USPQ 149 (see footnote 2).

The Examiner then alleges that "[t]he structural formula of claim 18 does not have a significant structural feature that is shared by all of its alternatives which is inventive". But then in the very next line the Examiner states "[t]he structure has only a pyrazolinone as common" structure.

Applicants respectfully traverse the improper Markush group rejection. Applicants direct the Examiner's attention to M.P.E.P. 803.02, which states in relevant part:

> "...it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention...Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility".

Applicants submit that the compounds of claim 18 possess unity of invention. The compounds of claim 18 share the common utility of being kinase inhibitors; and the compounds of Claim 18 share a substantial structural feature, namely the pyrazolinone, which is essential for the stated common utility. The Examiner recognizes that the pyrazolinone is a common structural feature of all the compounds claimed in claim 18. It is rather apparent that the pyrazolinone is an essential feature for inhibiting a kinase activity. Having met the two conditions set out for unity of invention, it is improper for the Office to reject claim 18 as being drawn to an improper Markush group.

Accordingly, the rejection of claims 18-21 and 23-45 under the judicially created doctrine of being drawn to an improper Markush group should be withdrawn and claims 18-21 and 23-45 be examined on its merits in its entirety.

The Examiner has rejected claims 18-21 and 23-45 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection. The following responses are numbered according to the paragraphs in the instant Office Action.

i) Applicants have amended claim 18 by replacing "and" with "or" as suggested by the Examiner.

ii) Applicants have amended the groups in variables "R" and "Z" so that they read as radicals rather than as molecules. With respect to the group "benzoindole", it is the name of the group wherein a benzene ring is fused to the phenyl part of an indole. Since the fusion of the benzene ring can be on any of the four carbons of the phenyl part of the indole, the term benzoindole covers three possible molecules. The term "azaindole" covers the molecule wherein there is an additional nitrogen atom in the pyrrole portion of the indole system. Since there are two positions where the additional nitrogen can be, the term covers two possible molecules. The term "triazine" is purposefully left unspecified since it is intended to cover all triazine species. i.e., "triazine" is used as a generic term to cover the different species of triazine.

iii) With respect to the term "substituted", Applicants submit that the definition of the term "substituted" is readily understood by one of ordinary skill in the art to include any substituent that is chemically stable when attached to the moiety that is being substituted. Applicants have discovered that irrespective of the substituents on the "substituted" moiety, the compound has the claimed utility. Therefore, Applicants' scope should not be hindered by a requirement to list all possible substituents.

iv) Applicants believe that the claim is clear. Claim 28 is directed to inhibiting a kinase with a compound of claim 18. This means that the inhibition could be done *in vitro* or *in vivo*. Which means that the inhibition could be in an *in vivo* therapeutic context or in an *in vitro* or *in vivo* assay context. Therefore, Applicants do not believe claim 28 requires amendment.

v) Applicants are unclear about the nature of the Examiner's perception of indefiniteness in this regard. The "recipient" is introduced as "a recipient", which means that claim 29 adds an additional element. In light of the explanation of what claim 28 is intended to cover, Applicants believe that claim 29 is clear and definite.

vi) Claim 37 is clear in that it claims any and all hyperproliferative disorders since there is no limitation of the term. How hyperproliferative disorders are affected is described at, *inter alia*, pages 89-94 of the instant application.

vii) Claim 38 is clear in that it claims any and all angiogenesis since there is no limitation of the term.

Based upon the foregoing, Applicants believe that the rejection of claims 18-21 and 23-45 under 35 U.S.C. §112, second paragraph, is obviated and should be withdrawn.

With regard to the Examiner's comment about claim 22, since claim 22 has been cancelled, without waiver or prejudice, the comment is obviated. However, Applicants note that Applicants do not agree with the Examiner's interpretation of M.P.E.P. 1.141(a).

Based upon the foregoing, Applicants believe that claims 18-21 and 23-45 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' attorney at the number noted below.

Date: May 15, 2002

Respectfully submitted,

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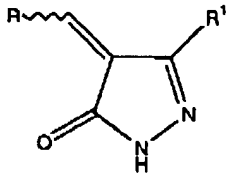
APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

18. (Amended) A compound represented by the following structural formula:



or [and] physiologically acceptable salts thereof, wherein:

R is selected from the group consisting of substituted or unsubstituted: indolyl[e], imidazolyl[e], 1,2,3-triazolyl[e], 1,2,4-triazolyl[e], benzimidazolyl[e], 4,5,6,7-tetrahydroindolyl[e], benzoindolyl[e], azaindolyl[e], indazolyl[e], pyridinyl[e], quinolinyl[e], pyrimidinyl[e], phenyl [benzene], pyrazinyl[e], pyrrolyl[e], pyrazolyl[e], oxazolyl[e] and thiazolyl[e];

R^1 is hydrogen or -A-Z;

A is $-(CH_2)_n-$, $-(CH_2)_nNH-$, $-(CH_2)_nO-$, $-(CH_2)_nS-$, $-(CH_2)_nS(O)-$ or $-(CH_2)_nS(O)_2-$;

Z is -H, a lower alkyl, aralkyl, trihalomethyl, trihalomethylcarbonyl, $R^3OC(O)-$, $-NR^4R^5$, $-C(O)NR^4R^5$, R^3CO-, R^3O-, or a ring system selected from the group consisting of a C_3-C_6 cycloalkyl[ane], isoxazolyl[e], isothiazolyl[e], imidazolyl[e], phenyl [benzene], pyrrolyl[e], indolyl[e], pyridinyl[e], pyrazinyl[e], pyrimidinyl[e], benzothiazolyl[e], tetrahydrofuranyl, thiophenyl[e], imidazolyl[e], furanyl, triazinyl[e], benzimidazolyl[e], pyridazinyl[e], quinoxalinyl[e], pyrazolyl[e], oxazolyl[e], thiazolyl[e] and the N-oxides thereof wherein said ring system can be optionally substituted with one or more moieties selected from the group consisting of halogens, lower alkyl, R^3O-, HO-, HOC(O)-, $R^3OC(O)-$, trihalomethyl, nitro, an aromatic group, a (C_3-C_6)cycloalkyl group, a heterocyclic group, an aralkyl group, a (C_3-C_6)cycloalkyl-alkyl group, a heterocyclyl-alkyl group, -CN, $-C(O)NR^4R^5$ or $-NR^4R^5$;

R^3 for each occurrence is, independently selected from the group consisting of substituted or unsubstituted: lower alkyl group, lower alkoxy lower alkyl group, aromatic group, (C_3-C_6)cycloalkyl group, heterocyclic group, aralkyl group, a (C_3-C_6)cycloalkyl-alkyl group, and heterocyclyl-alkyl group;

R^4 and R^5 for each occurrence are each, independently, hydrogen, or are selected from the group consisting of substituted or unsubstituted: lower alkyl group, aromatic group, (C_3-C_6)cycloalkyl group, heterocyclic group, aralkyl group, a (C_3-C_6)cycloalkyl-alkyl group, and heterocyclyl-alkyl group;

optionally, R^4 and R^5 together with the nitrogen to which they are attached represent morpholino, pyrrolidino, piperidino, imidazol-1-yl, piperazino, thiamorpholino, azepino or perhydro-1,4-diazepin-1-yl groups each optionally substituted by one or more moieties selected from the group consisting of lower alkyl, hydroxy, lower alkoxy lower alkyl, an aromatic group, a (C_3-C_6)cycloalkyl group, a heterocyclic group, an aralkyl group, a (C_3-C_6)cycloalkyl-alkyl group, and a heterocyclyl-alkyl group; and

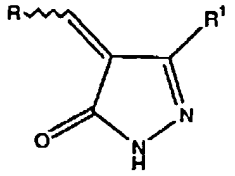
n is an integer from 0 to 3;

provided that when R is an unsubstituted indol-3-yl then R^1 is not $-NH_2$.

APPENDIX B

Claims

18. (Amended) A compound represented by the following structural formula:



or physiologically acceptable salts thereof, wherein:

R is selected from the group consisting of substituted or unsubstituted: indolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzimidazolyl, 4,5,6,7-tetrahydroindolyl, benzoindolyl, azaindolyl, indazolyl, pyridinyl, quinolinyl, pyrimidinyl, phenyl, pyrazinyl, pyrrolyl, pyrazolyl, oxazolyl and thiazolyl;

R^1 is hydrogen or -A-Z;

A is $-(CH_2)_n-$, $-(CH_2)_nNH-$, $-(CH_2)_nO-$, $-(CH_2)_nS-$, $-(CH_2)_nS(O)-$ or $-(CH_2)_nS(O)_2-$;

Z is -H, a lower alkyl, aralkyl, trihalomethyl, trihalomethylcarbonyl, $R^3OC(O)-$, $-NR^4R^5$, $-C(O)NR^4R^5$, R^3CO-, R^3O-, or a ring system selected from the group consisting of a C_3-C_6 cycloalkyl, isoxazolyl, isothiazolyl, imidazolyl, phenyl, pyrrolyl, indolyl, pyridinyl, pyrazinyl, pyrimidinyl, benzothiazolyl, tetrahydrofuranyl, thiophenyl, imidazolyl, furanyl, triazinyl, benzimidazolyl, pyridazinyl, quinoxalinyl, pyrazolyl, oxazolyl, thiazolyl and the N-oxides thereof wherein said ring system can be optionally substituted with one or more moieties selected from the group consisting of halogens, lower alkyl, R^3O-, HO-, HOC(O)-, $R^3OC(O)-$, trihalomethyl, nitro, an aromatic group, a (C_3-C_6)cycloalkyl group, a heterocyclic group, an aralkyl group, a (C_3-C_6)cycloalkyl-alkyl group, a heterocyclyl-alkyl group, -CN, $-C(O)NR^4R^5$ or $-NR^4R^5$;

R^3 for each occurrence is, independently selected from the group consisting of substituted or unsubstituted: lower alkyl group, lower alkoxy lower alkyl group, aromatic group, (C_3-C_6)cycloalkyl group, heterocyclic group, aralkyl group, a (C_3-C_6)cycloalkyl-alkyl group, and heterocyclyl-alkyl group;

R^4 and R^5 for each occurrence are each, independently, hydrogen, or are selected from the group consisting of substituted or unsubstituted: lower alkyl group, aromatic group, (C_3-C_6)cycloalkyl group, heterocyclic group, aralkyl group, a (C_3-C_6)cycloalkyl-alkyl group, and heterocyclyl-alkyl group;

optionally, R^4 and R^5 together with the nitrogen to which they are attached represent morpholino, pyrrolidino, piperidino, imidazol-1-yl, piperazino, thiamorpholino, azepino or perhydro-1,4-diazepin-1-yl groups each optionally substituted by one or more moieties selected from the group consisting of lower alkyl, hydroxy, lower alkoxy lower alkyl, an aromatic group, a (C_3-C_6)cycloalkyl group, a heterocyclic group, an aralkyl group, a (C_3-C_6)cycloalkyl-alkyl group, and a heterocyclyl-alkyl group; and

n is an integer from 0 to 3;

provided that when R is an unsubstituted indol-3-yl then R^1 is not $-NH_2$.

19. The compound of Claim 18 wherein:

A is -NH-, -O-, -S-, -S(O)- or $-S(O)_2-$; and

Z is cyclopropyl, 3-pyridyl or pyrazinyl.

20. The compound of Claim 18 wherein:

A is -O-; and

Z is ethyl, n-propyl or isopropyl.

21. The compound of Claim 18 wherein:

A is $-CH_2-$; and

Z is phenyl , wherein said phenyl is optionally substituted with one or more moieties selected from the group consisting of halogens, trihalomethyl, hydroxy, $-NR^4R^5$, nitro, $-CONR^4R^5$, lower alkyl group, R^3O-, $-C(O)OR^4$ and $-OC(O)R^4$.

23. The compound of Claim 18 wherein the compound is a mixture of stereoisomers.

24. The compound of Claim 23 wherein the stereoisomers are enantiomers.

25. The compound of Claim 24 wherein the stereoisomers are E and Z isomers.

26. The compound of Claim 18 wherein the compound is a mixture of structural isomers.

27. The compound of Claim 26 wherein the structural isomers are tautomers.

28. A method of inhibiting one or more protein kinase activities comprising the administration of a compound of Claim 18.

29. The method according to Claim 28 wherein said compound is administered to a recipient in need of having one or more protein kinase inhibited.

30. The method of Claim 29 wherein the compound is a mixture of stereoisomers.

31. The method of Claim 30 wherein the stereoisomers are enantiomers.

32. The method of Claim 30 wherein the stereoisomers are E and Z isomers.

33. The method of Claim 29 wherein the compound is a mixture of structural isomers.

34. The method of Claim 29 wherein the structural isomers are tautomers.

35. The method of Claim 29 wherein said protein kinase is a tyrosine kinase.

36. The method according to Claim 35 wherein said tyrosine kinase is selected from the group consisting of KDR, Flt-1, TIE-2, Lck, Src, fyn, Lyn, Blk, and yes.

37. A method of affecting hyperproliferative disorders in a recipient comprising the administration of a compound of Claim 18 to said recipient.

38. A method of affecting angiogenesis in a recipient comprising the administration of a compound of Claim 18 to said recipient.

39. A pharmaceutical composition comprising a compound of Claim 18 and a pharmaceutically acceptable carrier or diluent.

40. A pharmaceutical composition comprising a compound of Claim 22 and a pharmaceutically acceptable carrier or diluent.

41. A compound according to Claim 18 wherein R is substituted with one or more substituents, each independently selected from the group consisting of halogens, lower alkyl groups, R^3O-, hydroxy, HOC(O)-, $R^3OC(O)$-, $R^3OC(O)R^6$-, R^3OR^6-, trihalomethyl, trihalomethylcarbonyl, nitro, $-C(O)NR^4R^5$, $-NR^4R^5$, R^3CO-, $-(CH_2)_n-R^7$, $-C(O)(CH_2)_n-R^7$, $-C(O)-(CH_2)_n-C(O)-R^7$, $-O(CH_2)_nR^7$, $-C(O)NR^4(CH_2)_nR^7$, $-C(O)O(CH_2)_nR^7$, $-OC(O)(CH_2)_nR^7$, $-NR^4C(O)(CH_2)_nR^7$, $-R^6NR^4R^5$, $-R^6N(R^4)-R^6-R^7$, $-R^6N(R^6-R^7)_2$, $-R^6C(O)NR^4(CH_2)_nR^7$, $-R^6C(O)O(CH_2)_nR^7$, $-R^6OC(O)(CH_2)_nR^7$, $-R^6NR^4C(O)(CH_2)_nR^7$, $-R^6CH(C(O)OR^4)(NR^5C(O)R^4)$, an optionally substituted aryl and an optionally substituted aralkyl group;

wherein the optionally substituted aryl and optionally substituted aralkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, trihalomethyl, hydroxy, $-NR^4R^5$, nitro, $-CONR^4R^5$, lower alkyl group, R^3O-, $-C(O)OR^4$ and $-OC(O)R^3$;

R^6 is a lower alkyl group or an aryl group; and

R^7 is alkoxy, haloalkyl, lower alkyl piperazine, hydroxy, R^3O-, $R^3C(O)$- or $-NR^4R^5$.

42. A compound of Claim 41, wherein R is pyrrolyl, indolyl, azaindolyl, phenyl, pyrazolyl, imidazolyl, thienyl, 4,5,6,7-tetrahydroindolyl, or quinolinyl.

43. A compound of Claim 42, wherein R is pyrrol-2-yl, pyrrol-3-yl, indol-2-yl, indol-3-yl, azaindol-3-yl, pyrazol-4-yl, imidazol-2-yl, imidazol-4-yl, thien-2-yl or quinolin-5-yl.

44. A compound of Claim 18 or 43, wherein R^1 is trifluoromethyl, amino, cyclopropylamino, methyl, ethyl, propyl, isopropyl, cyclopropyl, 2-methylcyclopropyl, 2,2,3,3-tetramethylcyclopropyl, 2-phenylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-O-phenyl, -$(CH_2)_p$-O-(4-methoxyphenyl), -$(CH_2)_p$-O-(4-chlorophenyl), -$(CH_2)_p$-O-(4-methylphenyl), -$(CH_2)_p$-O-(3-methylphenyl), -$(CH_2)_p$-O-(4-phenylphenyl), -$(CH_2)_p$-O-(4-hydroxyphenyl), -$(CH_2)_p$-O-(4-nitrophenyl), -$(CH_2)_p$-O-(4-aminophenyl), -$(CH_2)_p$-O-(4-carbamoylphenyl), -$(CH_2)_p$-O-(4-methoxycarbonylphenyl), -NH-phenyl, -NH-(4-methoxyphenyl), -NH-(4-chlorophenyl), -NH-(4-fluorophenyl), -NH-(4-isopropylphenyl), isopropoxy, ethoxy, cyclopentyloxy, -$(CH_2)_p$-indolyl, -$(CH_2)_p$-pyridyl, -$(CH_2)_p$-benzothiazolyl, -$(CH_2)_p$-pyrrolyl, -$(CH_2)_p$-tetrahydrofuryl, -$(CH_2)_p$-pyrazinyl, -$(CH_2)_p$-furyl, -$(CH_2)_p$-thienyl, -$(CH_2)_p$-phenyl, -$(CH_2)_p$-isoxazolyl, -$(CH_2)_p$-(5-methylisoxazolyl), -$(CH_2)_p$-pyrimidinyl, -$(CH_2)_p$-pyridazinyl, -$(CH_2)_n$-C(O)-OMe, -$(CH_2)_n$-C(O)-OEt and benzyl optionally substituted with one or more of Cl, F, OMe, methyl or amino where p is an integer from 1 to 3.

45. A compound of Claim 44, wherein R is optionally substituted with one or more moieties selected from the group consisting of Br, Cl, F, aminomethyl, N,N-dimethylaminomethyl, carboxy, carboxymethyl, carboxyethyl, carbonylmethyl, carbonylethyl, methoxycarbonyl, ethoxycarbonyl, phenyl, 4-morpholinomethyl, -C(O)-O-$(CH_2)_2$-$N(Me)_2$, -C(O)-O-$(CH_2)_2$-$N(Et)_2$, -C(O)-O-CH_2-$N(Me)_2$, -C(O)-O-$(CH_2)_2$-$N(Me)_2$, -C(O)-NH-$(CH_2)_2$-$N(Me)_2$, -CH_2-NH-C(O)-CF_3 and an optionally substituted moiety selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl and phenyl, where said optionally substituted moiety is optionally substituted with one or more of Br, Cl, F, hydroxy, nitro, amino or lower alkyl.